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Predicting Risk of Cognitive Decline in Very Old Adults Using Three Models: The Framingham Stroke Risk Profile; the Cardiovascular Risk Factors, Aging, and Dementia Model; and Oxi-Inflammatory Biomarkers.

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Associations between the Framingham Stroke Risk Profile, the Cardiovascular risk factors, Aging and Dementia model, oxidative and inflammatory biomarkers and cognitive decline in the very old

Abbreviated title: Cardiovascular risk and cognition

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OBJECTIVES To examine the Framingham stroke risk profile (FSRP), the Cardiovascular Risk Factors, Aging and Dementia (CAIDE) risk score, and biomarkers of inflammation and oxidative stress for associations with cognitive decline using three different cohort studies of the very old. Also, to examine if incorporating these biomarkers with the risk scores can affect the association with cognitive decline.

DESIGN Three longitudinal, population based cohort studies.

SETTING Newcastle upon Tyne, UK, Leiden, The Netherlands and Lakes or Bay of Plenty District Health Board areas, New Zealand.

PARTICIPANTS At baseline there were 616 participants in the Newcastle 85+ Study, 444 participants in the Leiden 85-plus Study and 396 participants in the LiLACS NZ Study (non-Māori population only) to analyse.

MEASUREMENTS 1) FSRP, 2) CAIDE risk score, 3) oxi-inflammatory load: cumulative risk score of three blood biomarkers including homocysteine, interleukin-6 and C-reactive protein, representing levels of oxidative stress and inflammation and 4) FSRP incorporating the oxi-inflammatory load 5) CAIDE risk score incorporating the oxi-inflammatory load. The oxi-inflammatory load could only be calculated in the Newcastle 85+ Study and the Leiden 85-plus Study. Baseline and prospective measures of global cognitive function (MMSE©) were available for all three datasets. Domain specific measures (attention, speed and memory) were available for the Newcastle 85+ Study and the Leiden 85-plus Study.

RESULTS Meta-analysis of pooled results showed an increased risk of incident global cognitive impairment with higher FSRP (HR=1.46, 95%CI: 1.08 to 1.98), CAIDE (HR=1.53, 95%CI: 1.09 to 2.14) scores and oxi-inflammatory load (HR=1.73, 95%CI: 1.04 to 2.88).

Adding the oxi-inflammatory load to the risk scores increased the hazard ratios for the FSRP (HR=1.65, 95% CI: 1.17 to 2.33) and the CAIDE model (HR=1.93 (1.39 to 2.67).

CONCLUSION Incorporating the oxi-inflammatory load with cardiovascular risk scores may be useful for determining risk of future cognitive impairment in the very old.

Key words: cardiovascular risk, biomarkers, cognitive function, dementia, cognitive decline

Risk factors for cardiovascular disease (CVD) and stroke such as hypertension and high cholesterol have been associated with cognitive decline and dementia.[1] Many cardiovascular risk factors often co-occur, and risk prediction models have been developed to predict an individual's risk of future CVD or stroke, such as the Framingham Stroke Risk Profile (FSRP).[2] The Cardiovascular Risk Factors, Aging and Dementia (CAIDE) risk score was specifically developed for the midlife population to predict future risk of dementia based on cardiovascular and lifestyle factors.[3] Further, blood biomarkers, such as C-reactive protein, homocysteine and interleukin-6, are independent risk factors of CVD.[4]

Previous longitudinal studies have suggested an association between cardiovascular risk models and cognitive decline, but these studies have been conducted midlife and younger old populations.[5-12] This association has not yet been explored in the very old. Cardiovascular biomarkers, such as homocysteine, C-reactive protein and interleukin-6, have also been associated with cognitive decline[13-15]; however, previous research has also not focused on the very old.

Identifying individuals at the highest risk of dementia is important for developing targeted intervention strategies for the primary prevention of dementia. Determining risk of cognitive decline and dementia in dementia-free, cognitively healthy individuals is difficult due to the numerous risk factors that have been associated with dementia and individual variability as different populations, such as different age groups, may be differently affected by certain risk factors. Several dementia risk prediction models have been proposed and investigated in population-based longitudinal studies. Examples of risk prediction models for dementia include the Australian National University-Alzheimer's Disease Risk Index (ANU-ADRI), the CAIDE model and the Brief Dementia Screening Indicator. Further, the late-life dementia risk index was developed in an older population (mean age 76 years). Factors included in current dementia risk prediction models are wide-ranging and a recent systematic review

concluded that the current models available were not adequate for discriminating those who later developed dementia from those who did not develop dementia.[16]

Studying the very old presents a unique opportunity to identify factors that are still associated with cognitive impairment at the extreme end of ageing, and could be potential targets for intervention to maintain cognitive performance. Predicting what impacts cognitive health may also have implications regarding impact on healthy life expectancy.[17]

The objectives of this study were to determine if there was a prospective association between the FSRP,[18] the CAIDE risk model[3] or oxi-inflammatory load (a sum score of three different biomarkers: homocysteine, interleukin-6 and C-reactive protein) with cognitive function in very old individuals. Further, we examined whether combining the oxi-inflammatory load with the risk scores could affect the association with cognitive function. We used, population-based data from three of the largest cohort studies in this age group from different regions of the world including: the Newcastle 85+ Study (UK), the Leiden 85-plus Study (Netherlands) and The Life and Living in Advanced Age: A Cohort Study in New Zealand (LiLACS NZ) Study.

METHODS

All of the datasets used in this study are from longitudinal populations-based studies of health and ageing in the very old.

Newcastle 85+ Study

All adults born in 1921 who were permanently registered with a participating general practice in Newcastle upon Tyne and North Tyneside (North-East England) were invited to participate.[19, 20] A trained research nurse administered a multidimensional health assessment in the participant's usual place of residence. In total, of 1453 eligible people who were invited to participate, 845 had baseline data for both the detailed multidimensional health

assessment and general practice record review. For all analyses those with a history of stroke or dementia were excluded, in line with previous studies examining associations between the Framingham stroke risk profile and cognitive function.[21-23] 616 participants had complete clinical and laboratory data and no previous history of stroke or dementia at baseline. Follow-up assessments took place at 18, 36 and 60 months from baseline.[24]

Leiden 85-plus Study

Of the 705 residents of Leiden who turned 85 between September 1st 1997 and September 1st 1999 and who were eligible to participate, 599 responded and participated in the study.[25] 444 had complete clinical and laboratory data at baseline and no previous history of stroke or dementia at baseline and were included in this analysis. Participants were visited at their usual place of residence for a detailed health assessment and their medical records from their primary care physician were also reviewed. There were five follow-up assessments which took place annually.

LiLACS NZ Study

The cohort was derived from two separate populations including Māori (indigenous people in NZ) and non-Māori.[26] This study only includes the non-Māori cohort aged 85 at baseline to allow comparison with the other included cohorts. Individuals born between January 1st and December 31st 1925 and who resided within the Lakes or Bay of Plenty District Health Board areas when the study enrolment was completed in 2010 were recruited. Of the 870 eligible non-Māori individuals whom were identified, 516 enrolled in the study.[27] 396 had complete clinical and laboratory data at baseline and no previous history of stroke or dementia at baseline and were included in this analysis. Participants were given the choice to meet at their usual place of residence or at another site for a structured face-to-face standardised questionnaire, a detailed health assessment and a review of general practice medical records. There were three follow-up assessments that took place annually.

Assessment of the risk prediction models

The FSRP and the CAIDE models were determined in each study using baseline data. Supplementary Table 1 shows the variables included in each model and their measurement. All variables, with the exception of education and physical activity, were measured similarly across the cohorts. APOE4 was not available for the LiLACS NZ dataset. For analysis, FSRP and CAIDE scores were divided into study-specific tertiles to create low, intermediate and high-risk groups, with the low-risk group used as the reference category.[11, 28]

Biomarkers and Oxi-inflammatory load

Three biomarkers previously shown to be associated with cardiovascular diseases were selected from the blood results, including two inflammatory biomarkers (i.e., C-reactive protein (CRP) and interleukin-6) and one biomarker for oxidative stress (i.e., homocysteine).[4] Details of the biomarker assays in each study can be found in the supplementary material. As the distribution of the biomarkers was skewed the data were log transformed. A fixed value of 0.1 was added to each data point including zero values to calculate the logarithmic value. In order to determine the combined effect of all three biomarkers a cumulative score of the standardised z-scores for each log transformed biomarker value was created, this will be referred to as a participant's "oxi-inflammatory load". Homocysteine was not available for the LiLACS NZ dataset and so the cumulative score could not be calculated in this cohort.

As in previous analyses, the biomarkers and the oxi-inflammatory load scores were grouped into deciles and participants were allocated to one of three groups: $<10^{th}$ percentile, 10^{th}-90^{th} percentile or $>90^{th}$ percentile and the middle category was used as the reference.[29] A sensitivity analysis grouping the oxi-inflammatory load scores into three tertile groups (with the middle category used as the reference) was also conducted.

To examine whether the oxi-inflammatory load scores could enhance the prediction of cognitive impairment of the FSRP or the CAIDE scores, further analyses were run by adding points to the CAIDE or FSRP scores based on the oxi-inflammatory load values of the participants. 6 points were added to the FSRP or CAIDE score for the highest tertile for the oxi-inflammatory load scores, 3 points were added for the middle tertile and 0 points were added for the highest tertile.

Cognitive assessment

Global cognitive function was assessed in all three cohorts using the standard Mini-Mental State Examination (MMSE©), with scores ranging from 0 to 30.[30] The MMSE© was conducted at baseline, 36 months and 60 months in the Newcastle 85+ Study, at baseline and annually for five years in the Leiden 85-plus Study, and at baseline and annually for three years in the LiLACS NZ Study. For the MMSE©, cognitive impairment at baseline and incident cognitive impairment at each follow-up was defined using a cut off score of ≤25 points.

Domain specific cognitive functions including attention, information processing and episodic verbal recognition memory were assessed in the Newcastle 85+ Study using the Cognitive Drug Research (CDR) System. Details of the cognitive assessments in the Newcastle 85+ Study have been published elsewhere[31]. The CDR System was conducted at baseline, 18 months and 36 months.

In the Leiden 85-plus Study, speed was measured using the Letter Digit Coding Test. Attention was measured using the Stroop test part 3. Memory was measured using the 12 word learning test. These tests were administered at baseline and annually for five years. There were no domain-specific tests completed in the LiLACS NZ Study.

Statistical analysis

Cox proportional hazards models were run to determine whether the FSRP and CAIDE scores or the oxi-inflammatory load were associated with the occurrence of impairments in global or domain specific cognitive function (dichotomised variables) over the follow-up period in each study. Tests of the proportional hazards assumption were run for each model and were not violated. Biomarker models were adjusted for potential confounding factors including sex, years of education, current alcohol consumption and smoking status.

Following this, a meta-analysis of the highest HR category was conducted to estimate the pooled effects of the FSRP, CAIDE and oxi-inflammatory load scores on prospective risk of impaired global cognitive function (i.e., MMSE© scores). HR and 95% confidence intervals (95%CI) for each study were entered into the models. Statistical heterogeneity was assessed using the I^2 and the Q tests and a $P<.10$ was chosen as a cut-off for heterogeneity.[32] A fixed-effect model was applied as a result of the lack of heterogeneity (Q test, $P>.10$) and Forest plots were generated for the FSRP, CAIDE and oxi-inflammatory load scores. Comprehensive Meta-Analysis 2 software (Biostat, Engelwood, New Jersey) was used to conduct the analysis.

Linear mixed models were used to examine change in the continuous test scores for each cognitive measure. Cognitive test scores that were positively skewed (i.e. PoA, SRT, Stroop Test Part 3) were logarithmically transformed, and MMSE© scores (which were negatively skewed) were corrected using the following formula NEWX=SQRT(K-X) where K is the maximum score. Each model included the risk model or biomarker score (cross-sectional effect), time (change in cognitive scores over time) and an interaction term between the risk model or biomarker score and time (additional effect of the risk model or biomarker score). All data were analysed using Stata v.13.0 (Stata Corp LP, College Station, TX, USA).

RESULTS

After excluding participants with a history of stroke or dementia at baseline the analytical sample included 616 participants in the Newcastle 85+, 444 in the Leiden 85-plus and 396 in the LiLACS NZ studies. The baseline characteristics of each sample are shown in Table 1.

The Framingham stroke risk profile

Global cognitive function

For the individual studies, the hazard ratios for an increased risk of impaired global cognitive function were all above one for the highest FSRP groups (Table 2). Meta-analysis of pooled results showed an increased risk of impaired global cognitive function with a higher FSRP (MMSE©: HR=1.46, 95%CI: 1.08 to 1.98, *P*=.01). However, in the linear mixed models the associations between the FSRP and global cognitive function (cross-sectional results) or global cognitive decline were all *P*>.05 (Supplementary Table 2).

Domain specific cognitive function

Upon examining the specific cognitive domains, which are only available for the Newcastle 85+ and Leiden 85-plus studies, higher FSRP scores were associated with an increased risk of impaired speed for the Newcastle 85+ Study (SRT: HR=1.42; 95%CI: 1.06 to 1.91, *P*=.02) (Table 4). In the linear mixed models the FSRP was cross-sectionally associated with speed scores for the Leiden 85-plus Study only (LDCT: (B (SE)=-2.19 (0.913), *P*=.02) (Table 5).

The CAIDE model

Global cognitive function

Higher CAIDE scores were associated with an increased risk of impaired global cognitive function in the meta-analysis of pooled MMSE© results (HR=1.46, 95%CI: 1.05 to 2.02, *P*=.02). For the linear mixed model results, the CAIDE model was cross-sectionally

associated with global cognitive function in the Leiden 85-plus Study (B (SE)=0.493 (0.112), *P*<.001) and the LiLACS NZ Study (B (SE)=0.348 (0.109), *P*=.001).

Domain specific cognitive function

The CAIDE model was not longitudinally associated with any of the domain specific cognitive test results for the Newcastle 85+ or Leiden 85-plus studies for the Cox proportional hazard models or the linear mixed models. However, the linear mixed models showed the CAIDE model was cross-sectionally associated with speed, attention and memory scores for the Leiden 85-plus Study.

Oxi-inflammatory load

Global cognitive function

A higher oxi-inflammatory load was associated with incident global cognitive impairment in the meta-analysis of pooled results (Newcastle 85+ Study and Leiden 85-plus Study only: HR=1.73, 95%CI: 1.04 to 2.88, *P*=.04) (Figure 1). In the linear mixed models, the oxi-inflammatory load was not longitudinally associated with global cognitive decline, but a cross-sectional association was observed between a higher oxi-inflammatory load and poorer global cognitive function scores at baseline (B (SE)=0.320 (0.127), *P*=.01) in the Leiden 85-plus Study.

Domain specific cognitive function

A higher oxi-inflammatory load was associated with an increased risk of incident impairment of attention in both the Newcastle 85+ (HR=1.58; 95%CI: 1.05 to 2.36, *P*=.03), and Leiden 85-plus studies (HR=2.18; 95%CI: 1.27 to 3.74, *P*=.01) (Table 3). Further, a higher oxi-inflammatory load was also associated with an increased risk of impairment of speed in the Newcastle 85+ Study (HR=1.85; 95%CI: 1.24 to 2.75, *P*=.003), but this association was not observed in the Leiden study. In the linear mixed models, a higher oxi-inflammatory load was not longitudinally associated with any of the domain specific cognitive test results for the

Newcastle 85+ or Leiden 85-plus studies. However, the linear mixed models showed a higher oxi-inflammatory load was cross-sectionally associated with better attention scores for the Newcastle 85+ Study (B (SE)=0.058 (0.028), *P*=.04) (Table 4).

Adding the oxi-inflammatory load to the FSRP and CAIDE model

In order to determine if the oxi-inflammatory load could be used to improve the prediction of the FSRP or CAIDE models we added the oxi-inflammatory load scores to the FSRP and CAIDE scores as described in the methods. In the meta-analysis of pooled results (Newcastle 85+ Study and Leiden 85+ Study only), adding the oxi-inflammatory load scores improved the prediction of both the CAIDE (HR for CAIDE and oxi-inflammatory load=1.93; 95% CI: 1.39 to 2.67, *P*<.001 and FSRP scores (HR for FSRP and oxi-inflammatory load=1.65; 95% CI: 1.17 to 2.33, *P*<.001).

Sensitivity Analysis

The Leiden 85-plus dataset did not have years of education, but the education measure was based on the education system in the Netherlands, therefore we re-ran the analysis of the CAIDE score and excluded education from its calculation in order to examine if differences in the operationalization of education was the reason for the discrepant results between the studies. When education was excluded the result changed and the CAIDE score was no longer associated with global cognitive impairment (Leiden 85-plus: HR for the highest risk tertile compared to the lowest=1.25, 95%CI: 0.81 to 1.92, *P*=.30).

Analyses for the Cox proportional hazard models were repeated using tertiles for the oxi-inflammatory load (middle category as reference) (MMSE©: HR=1.36, 95%CI: 0.96 to 1.92, *P*=.07).

DISCUSSION

In three prospective studies of individuals aged 85 years, free of stroke or dementia at baseline, from the UK, the Netherlands and New Zealand, we found that higher FSRP and CAIDE risk scores or a higher oxi-inflammatory load, derived from a cumulative score of three cardiovascular biomarkers, were associated with incident global impairment. Further, incorporating the oxi-inflammatory load scores in to the FSRP or CAIDE model improved the ability of the risk models to predict incident global cognitive impairment. However, this could only be determined using the Newcastle 85+ Study and the Leiden 85-plus Study data as the LiLACS NZ Study does not have homocysteine measures needed to determine the oxi-inflammatory load.

Several longitudinal studies have found both the Framingham and the CAIDE risk models to (for a review of studies see).[21] When investigating specific cognitive domains, the results have however been inconsistent with regards to which cognitive domains may be affected by higher cardiovascular risk.[5-8, 11, 33] Yet, the majority of studies have focused on the midlife and younger old populations, and no study has previously looked at the association between cardiovascular risk models and cognitive function in the very old.

Studies in relatively younger populations have found that homocysteine, interleukin-6 and C-reactive protein predict cognitive decline.[13-15] Previous findings in the Newcastle 85+ Study have shown cross-sectional associations between these biomarkers and global cognitive impairment measured using the MMSE©.[29] Similarly, previous findings in the Leiden 85-plus Study have also shown cross-sectional associations between homocysteine and cognitive impairment, but this association was not found with rate of cognitive decline.[34]

In this study, higher levels of biomarkers for oxidative stress and inflammation were longitudinally associated with an increased risk of developing global and domain specific

cognitive (speed and attention) impairment. Biomarkers of cardiovascular risk may be useful for identifying those at risk of future cognitive impairment as oxidative stress and inflammation are also implicated in the pathophysiology of dementia. It is widely accepted that increasing levels of oxidative stress and impaired cellular functions linked to abnormal protein accumulation and modification of molecular structures may have direct effects on neuronal structure and integrity, affecting cognitive function.[35] Further, inflammation is thought to be a key factor in neurodegeneration, contributing to the development of some of the classic hallmarks of Alzheimer's pathology such as amyloid-beta plaques.[36] These findings have been formalised in the theory of inflammaging as a critical factor in the pathogenesis of age-related chronic cardiovascular and neurodegenerative diseases.[37, 38]

Current dementia risk prediction models are not sufficient for detecting those at greatest risk of developing cognitive impairment or dementia[16]. Factors included in current dementia risk prediction models include demographic factors (e.g., age, sex, ethnicity), subjective cognitive complaints, functioning (as measured by Activities of daily living (ADLs) scales), neuropsychological test scores, health related measures (e.g., history of cardiovascular disease, body mass index), lifestyle measures (e.g., smoking status, alcohol intake), dietary related factors (e.g., folic acid and fish intake), magnetic resonance imaging (MRI) results (e.g., white matter disease) and others (e.g., family history of dementia). The best models were described as those which incorporated a diverse range of risk factors into the models, but it is most likely that there will not be one model which is suitable for all populations and different dementia risk models may need to be developed for different populations (e.g., based on age group)[39]. To date, no such dementia risk model has been validated in a very old population. Development of a highly accurate model for discriminating those at high-risk of future dementia from those at medium and low-risk would be needed before screening the older population for future risk of dementia in primary care practice could become a

possibility. Incorporation of the biomarkers investigated in this study with the classical cardiovascular risk factors of the FSRP or CAIDE models may be useful to investigate when developing a dementia risk prediction model for the very old.

There are both strengths and limitations to this study. The Newcastle 85+, Leiden 85-plus and LiLACS NZ cohorts are prospective longitudinal cohort studies of the very old and this is the first study that has aggregated data from all three cohorts.

There are some limitations, the LiLACS NZ Study did not have homocysteine levels needed to create the oxi-inflammatory load and therefore, the findings for the oxi-inflammatory load are based on the Newcastle 85+ and Leiden 85-plus studies only.

Results were not always consistent across the studies and discrepancies in results between studies may be due to: 1) differences in the assays used to determine C-reactive protein and interleukin-6 across the two studies, since the Leiden 85-plus Study used less sensitive assays which led to the attribution of values of zero for results lower than the limit of detection (number of zero values: C-reactive protein=82, interleukin-6=119), 2) differences in the cohorts themselves, for instance, education levels varied widely, the Leiden Study did not have years of education needed to correctly determine the CAIDE scores, the LiLACS Study did not have APOE4 required for the CAIDE model, differences in the cognitive tests used to asses domain-specific cognitive function and the smaller sample size of the Leiden 85-plus Study and LiLACS NZ Study, 3) a cohort effect related to differences in birth year between cohorts: [1913-1915 (Leiden 85-plus Study), 1921 (Newcastle 85+ Study) and 1925 (LiLACS NZ Study)].

Further research in very old age groups is needed to gain a full understanding of the association between the Framingham models, the CAIDE models or cardiovascular biomarkers and cognitive decline. In particular with respect to which cognitive domains may be most likely to be affected.

There is currently no recommended tool for identifying those at risk of developing cognitive impairment or dementia in the very old population.[16] Combining the oxi-inflammatory load with the FSRP or the CAIDE model may further improve the ability of these models to predict cognitive changes. Biomarkers would be relatively easy to measure in a clinical setting and could potentially provide clinicians with an overview of a patient's cardiovascular health in addition to their future risk for cognitive impairment. Intervention strategies to reduce the oxi-inflammatory load could potentially target both improvements in cardiovascular health and cognitive function.

REFERENCES

[1] Duron E, Hanon O. Vascular risk factors, cognitive decline, and dementia. *Vascular health and risk management*. 2008;**4**: 363-381.

[2] D'Agostino RB, Sr., Vasan RS, Pencina MJ*, et al.* General cardiovascular risk profile for use in primary care: the Framingham Heart Study. *Circulation*. 2008;**117**: 743-753.

[3] Kivipelto M, Ngandu T, Laatikainen T, Winblad B, Soininen H, Tuomilehto J. Risk score for the prediction of dementia risk in 20 years among middle aged people: a longitudinal, population-based study. *The Lancet Neurology*. 2006;**5**: 735-741.

[4] Vasan RS. Biomarkers of cardiovascular disease: molecular basis and practical considerations. *Circulation*. 2006;**113**: 2335-2362.

[5] Brady CB, Spiro A, 3rd, McGlinchey-Berroth R, Milberg W, Gaziano JM. Stroke risk predicts verbal fluency decline in healthy older men: evidence from the normative aging study. *The journals of gerontology Series B, Psychological sciences and social sciences*. 2001;**56**: P340-346.

[6] Kaffashian S, Dugravot A, Brunner EJ*, et al.* Midlife stroke risk and cognitive decline: A 10-year follow-up of the Whitehall II cohort study. *Alzheimers & Dementia*. 2013;**9**: 572-579.

[7] Kaffashian S, Dugravot A, Elbaz A*, et al.* Predicting cognitive decline: a dementia risk score vs. the Framingham vascular risk scores. *Neurology*. 2013;**80**: 1300-1306.

[8] Kaffashian S, Dugravot A, Nabi H*, et al.* Predictive utility of the Framingham general cardiovascular disease risk profile for cognitive function: evidence from the Whitehall II study. *European heart journal*. 2011;**32**: 2326-2332.

[9] Dregan A, Stewart R, Gulliford MC. Cardiovascular risk factors and cognitive decline in adults aged 50 and over: a population-based cohort study. *Age Ageing*. 2013;**42**: 338-345.

[10] Kelley BJ, McClure LA, Letter AJ*, et al.* Report of stroke-like symptoms predicts incident cognitive impairment in a stroke-free cohort. *Neurology*. 2013;**81**: 113-118.

[11] Laughlin GA, McEvoy LK, von Muhlen D*, et al.* Sex differences in the association of Framingham Cardiac Risk Score with cognitive decline in community-dwelling elders without clinical heart disease. *Psychosomatic medicine*. 2011;**73**: 683-689.

[12] Unverzagt FW, McClure LA, Wadley VG*, et al.* Vascular risk factors and cognitive impairment in a stroke-free cohort. *Neurology*. 2011;**77**: 1729-1736.

[13] Economos A, Wright CB, Moon YP*, et al.* Interleukin 6 plasma concentration associates with cognitive decline: the northern Manhattan study. *Neuroepidemiology*. 2013;**40**: 253-259.

[14] Komulainen P, Lakka TA, Kivipelto M*, et al.* Serum high sensitivity C-reactive protein and cognitive function in elderly women. *Age Ageing*. 2007;**36**: 443-448.

[15] Haan MN, Miller JW, Aiello AE*, et al.* Homocysteine, B vitamins, and the incidence of dementia and cognitive impairment: results from the Sacramento Area Latino Study on Aging. *The American journal of clinical nutrition*. 2007;**85**: 511-517.

[16] Stephan BC, Kurth T, Matthews FE, Brayne C, Dufouil C. Dementia risk prediction in the population: are screening models accurate? *Nature reviews Neurology*. 2010;**6**: 318-326.

[17] Leist KA. *Health and cognition in old age : from biomedical and life course factors to policy and practice*.

[18] Wolf PA, D'Agostino RB, Belanger AJ, Kannel WB. Probability of stroke: a risk profile from the Framingham Study. *Stroke; a journal of cerebral circulation*. 1991;**22**: 312-318.

[19] Collerton J, Davies K, Jagger C*, et al.* Health and disease in 85 year olds: baseline findings from the Newcastle 85+ cohort study. *Bmj*. 2009;**339**: b4904.

[20] Davies K, Collerton JC, Jagger C*, et al.* Engaging the oldest old in research: lessons from the Newcastle 85+ study. *BMC geriatrics*. 2010;**10**: 64.

[21] Harrison SL, Ding J, Tang EY*, et al.* Cardiovascular disease risk models and longitudinal changes in cognition: a systematic review. *PLoS One*. 2014;**9**: e114431.

[22] Elias MF, Sullivan LM, D'Agostino RB*, et al.* Framingham stroke risk profile and lowered cognitive performance. *Stroke; a journal of cerebral circulation*. 2004;**35**: 404-409.

[23] Llewellyn DJ, Lang IA, Xie J, Huppert FA, Melzer D, Langa KM. Framingham Stroke Risk Profile and poor cognitive function: a population-based study. *BMC neurology*. 2008;**8**: 12.
[24] Davies K, Kingston A, Robinson L*, et al.* Improving retention of very old participants in longitudinal research: experiences from the newcastle 85+ study. *PLoS One*. 2014;**9**: e108370.
[25] der Wiel AB, van Exel E, de Craen AJ*, et al.* A high response is not essential to prevent selection bias: results from the Leiden 85-plus study. *Journal of clinical epidemiology*. 2002;**55**: 1119-1125.
[26] Hayman KJ, Kerse N, Dyall L*, et al.* Life and living in advanced age: a cohort study in New Zealand--e Puawaitanga o Nga Tapuwae Kia Ora Tonu, LiLACS NZ: study protocol. *BMC geriatrics*. 2012;**12**: 33.
[27] Kerse N, Teh R, Moyes SA*, et al.* Cohort Profile: Te Puawaitanga o Nga Tapuwae Kia Ora Tonu, Life and Living in Advanced Age: a Cohort Study in New Zealand (LiLACS NZ). *International journal of epidemiology*. 2015.
[28] de Ruijter W, Westendorp RG, Assendelft WJ*, et al.* Use of Framingham risk score and new biomarkers to predict cardiovascular mortality in older people: population based observational cohort study. *Bmj*. 2009;**338**: a3083.
[29] Martin-Ruiz C, Jagger C, Kingston A*, et al.* Assessment of a large panel of candidate biomarkers of ageing in the Newcastle 85+ study. *Mechanisms of ageing and development*. 2011;**132**: 496-502.
[30] Molloy DW, Standish TI. A guide to the standardized Mini-Mental State Examination. *International psychogeriatrics / IPA*. 1997;**9 Suppl 1**: 87-94; discussion 143-150.
[31] Granic A, Hill TR, Kirkwood TB*, et al.* Serum 25-hydroxyvitamin D and cognitive decline in the very old: the Newcastle 85+ Study. *Eur J Neurol*. 2015;**22**: 106-115, e106-107.
[32] Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *Bmj*. 2003;**327**: 557-560.
[33] Reijmer YD, van den Berg E, van Sonsbeek S*, et al.* Dementia Risk Score Predicts Cognitive Impairment after a Period of 15 Years in a Nondemented Population. *Dementia and Geriatric Cognitive Disorders*. 2011;**31**: 152-157.
[34] Mooijaart SP, Gussekloo J, Frolich M*, et al.* Homocysteine, vitamin B-12, and folic acid and the risk of cognitive decline in old age: the Leiden 85-Plus study. *The American journal of clinical nutrition*. 2005;**82**: 866-871.
[35] Luque FA, Jaffe SL. The molecular and cellular pathogenesis of dementia of the Alzheimer's type an overview. *International review of neurobiology*. 2009;**84**: 151-165.
[36] Gorelick PB. Role of inflammation in cognitive impairment: results of observational epidemiological studies and clinical trials. *Annals of the New York Academy of Sciences*. 2010;**1207**: 155-162.
[37] Baylis D, Bartlett DB, Patel HP, Roberts HC. Understanding how we age: insights into inflammaging. *Longevity & healthspan*. 2013;**2**: 8.
[38] Franceschi C, Bonafe M, Valensin S*, et al.* Inflamm-aging. An evolutionary perspective on immunosenescence. *Annals of the New York Academy of Sciences*. 2000;**908**: 244-254.
[39] Tang EY, Harrison SL, Errington L*, et al.* Current Developments in Dementia Risk Prediction Modelling: An Updated Systematic Review. *PLoS One*. 2015;**10**: e0136181.

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The Newcastle 85+ Study was approved by the Newcastle and North Tyneside 1 research ethics committee. The Leiden 85-plus Study was approved by the Medical Ethics Committee of the Leiden University Medical Centre. The Northern X Regional Ethics Committee of New Zealand granted ethical approval for the LiLACS NZ Study in December 2009.

Conflict of interest

KAW has specified relationships with Bracket Global and Wesnes Cognition Ltd that might have an interest in the submitted work in the previous 3 years. SLH, AJMD, NK, RT, AG,

KD, WPJD, JG, TBLK, LR, CJ, MS and BCMS have no interests that may be relevant to the submitted work.

Author Contributions

SLH affirms they have listed everyone as an author who contributed significantly. SLH was responsible for conception, design and drafting of the manuscript, statistical analysis and interpretation of results. AJMD was the co-principal investigator of the Leiden 85-plus Study was responsible for providing support with the statistical analysis and interpretation of results and critical review of the manuscript. NK is the leader of the LILACS NZ cohort study and critically reviewed the manuscript. RT was responsible for critical review of the manuscript. AG was responsible for critical review of the manuscript. KD was responsible for the design of the Newcastle 85+ Study and critical review of the manuscript. KAW developed the CDR system and supplied the system to the Newcastle 85+ study and critically reviewed the manuscript. WPJD was responsible for critical review of the manuscript. JG is the co-principal investigator of the Leiden 85-plus Study and was responsible for critical review of the manuscript. TBLK is the principal investigator of the Newcastle 85+ Study and critically reviewed the manuscript. LR critically reviewed the manuscript. CJ was responsible for the design of the Newcastle 85+ Study, conception and design of the manuscript, interpretation of results and critical review of the manuscript. MS was responsible for conception and design of the manuscript and interpretation of results and critical review of the manuscript. BCMS was responsible for conception and design of the manuscript, interpretation of results and critical review of the manuscript.

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The funding sources had no role in the preparation of this paper.

FIGURE LEGENDS

Figure 1: Forest plots to show the pooled risk for impaired global cognitive function, measured by MMSE© in all three cohorts, associated with higher Cardiovascular risk factors, Aging and Dementia model (CAIDE) and Framingham stroke risk profile (FSRP) risk scores and oxi-inflammatory load.

Table 1. Baseline characteristics of participants in the Newcastle 85+, Leiden 85-plus Study and the LiLACS NZ studies used in this analysis (excluding those with dementia or stroke at baseline).

Characteristic	**Study**		
Risk model components	Newcastle 85+ study (n=616)	Leiden 85-plus Study (n=444)	LiLACS NZ (n=396)
Male, %	39.9	34.6	48.0
Systolic blood pressure (mmHg), mean (SD)	151.4 (23.5)	155.2 (18.7)	151.6 (22.8)
Total cholesterol (mg/dl), mean (SD)	192.0 (48.0)	220.8 (43.7)	199.8 (41.8)
Body mass index (kg/m²), mean (SD)	24.5 (4.4)	27.1 (4.5)	26.5 (4.3)
Blood pressure lowering drugs, %	70.8	43.9	60.4
Current smoker, %	5.3	16.0	5.1
Diabetes, %	18.2	13.9	13.1
Atrial Fibrillation, %	14.2	9.1	12.2
History of CVD, %	38.7	33.6	42.2
Physical activity, active, %	44.0	29.0	37.7
Education <10 years or low category, %	64.0	72.0	27.0
Risk models			
FSRP score (all), mean (SD)	19.5 (3.6), range 11-33	19.1 (3.8), range 10-33	18.9 (3.7), range 10-31
Low, %	42.2	34.3	33.7
Medium, %	25.0	34.8	36.2
High, %	32.5	30.9	30.1
CAIDE score (all), mean (SD)	8.5 (1.9), range 4-13	10.2 (1.7), range 4-15	7.9 (1.8), range 4-13
Low, %	48.7	59.3	48.4
Medium, %	24.3	16.8	34.2
High, %	27.0	23.9	17.4
Biomarkers			
Homocysteine (µmol/L), median (IQR)	16.7 (7.9)	12.5 (5.5)	-
Interleukin 6 (ng/mL), median (IQR)	19.7 (20.6)	10.0 (53.0)	2.3 (1.0)
C-reactive protein (mg/L), median (IQR)	2.5 (4.9)	3.0 (7.0)	2.9 (4.2)

Oxi-Inflammatory Load, mean (SD)	-0.1 (2.0)	-0.1 (2.0)	0.1 (1.7)
Cognitive function scores			
Global cognitive function, median (IQR)	27.3 (2.8)	27.0 (4.0)	27.0 (3.2)
Memory, median (IQR)	0.6 (0.2)	0.2 (1.8)	-
Attention, median (IQR)	1521.8 (290.3)	74.8 (37.9)	-
Speed, median (IQR)	417.6 (149.6)	16.0 (9.0)	-

The CAIDE score for LiLACS NZ study does not include ApoE4. Oxi-inflammatory load for LiLACS NZ study is only based on interleukin-6 and C-reactive protein. Education for the Leiden 85-plus Study is not based on years of education, but is determined by the categorizations of education used in the Leiden 85-plus Study. Abbreviations: CAIDE, Cardiovascular risk factors, Aging and Dementia model; CVD, cardiovascular disease; FSRP, Framingham stroke risk profile; IQR, interquartile range; SD, standard deviation. Newcastle 85+: Memory was measured using the sensitivity index for recognition ability (SI), attention was measured using power of attention (PoA) and speed was measured using simple reaction time (SRT), all part of the Cognitive Drug Research (CDR) computerised assessment system. Leiden 85-plus Study: Memory was measured using the Word-Learning Test, Immediate and Delayed Recall (based on sum of z scores), attention was measured using the Stroop Test Part 3 and speed was measured using the Letter Digit Coding Test. Numbers exclude people with dementia or stroke at baseline.

Table 2. Cox proportional hazard model results (HR and 95%CI) of the association between the FSRP, the CAIDE models, oxi-inflammatory load and incident global cognitive impairment after follow-up for the Newcastle 85+ study, Leiden 85-plus Study and LiLACS NZ cohorts.

	Meta-analysis		**Newcastle 85+ study**		**Leiden 85-plus Study**		**LiLACS NZ Study**	
	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
Global cognitive function								
FSRP								
Low	1.0		1.0		1.0		1.0	
Medium			0.95 (0.57, 1.59)	.85	0.99 (0.65, 1.53)	.97	1.56 (0.64, 3.77)	.33
High	**1.46 (1.08, 1.98)**	**.01**	1.15 (0.71, 1.86)	.56	1.44 (0.93, 2.22)	.10	**3.53 (1.44, 8.63)**	**.01**
CAIDE								
Low	1.0		1.0		1.0		1.0	
Medium			0.83 (1.50, 0.46)	.54	**1.84 (1.14, 2.96)**	**.01**	**2.43 (1.13, 5.22)**	**.02**
High	**1.53 (1.09, 2.14)**	**.01**	1.14 (0.64, 2.03)	.65	**1.64 (1.04, 2.58)**	**.03**	**2.87 (0.97, 8.47)**	**.06**
Oxi-inflammatory load								
Low	1.0		1.02 (0.53, 1.96)	.95	0.65 (0.31, 1.35)	.25	-	
Medium			1.0		1.0		-	
High	**1.73 (1.04, 2.98)**	**.04**	**2.13 (1.08, 4.20)**	**.03**	1.32 (0.61, 2.86)	.48	-	
CAIDE + oxi-inflammatory load								
Low	1.0		1.0		1.0		-	
Medium			1.38 (0.77, 2.46)	.28	1.28 (0.83, 1.97)	0.26	-	
High	**1.93 (1.39, 2.67)**	**<.001**	**1.96 (1.27, 3.42)**	**.02**	**1.89 (1.18, 3.02)**	**.008**	-	
FSRP + oxi-inflammatory load								
Low	1.0		1.0		1.0		-	
Medium			1.20 (0.75, 1.93)	.45	1.36 (0.88, 2.09)	.17	-	
High	**1.65 (1.17, 2.33)**	**<.001**	1.59 (0.94, 2.69)	.08	**1.70 (1.08, 2.68)**	**.02**	-	

Abbreviations: CAIDE, Cardiovascular risk factors, Aging and Dementia model; CVD, cardiovascular disease; FSRP, Framingham stroke risk profile. Global cognitive function measured by the Mini-Mental State Examination (MMSE) in all studies. Oxi-inflammatory load represents a sum score of the three biomarkers: standardised z-scores for each log transformed biomarker were calculated and the sums of these scores were then determined to create an oxi-inflammatory load. Categories based on tertiles for the FSRP and CAIDE models and for the oxi-inflammatory load: low represents <10th percentile, middle represents 10th-90th percentile and high represents >90th percentile. Impairment is ≤25 points on the MMSE for global cognitive function. Oxi-inflammatory load models adjusted for sex, years of education, current alcohol consumption and smoking status.

Table 3. Linear mixed model results (β (SE) P-value) of the association between the FSRP, the CAIDE model, oxi-inflammatory load and cognitive decline after follow-up for the Newcastle 85+ Study, Leiden 85-plus Study and LiLACS NZ cohorts

	Newcastle 85+ Study			**Leiden 85-plus Study**			**LiLACS NZ Study**		
	B (SE) *P*-value			B (SE) *P*-value			B (SE) *P*-value		
	Cross-sectional	Change over time	Change due to the risk model	Cross-sectional	Change over time	Change due to the risk model	Cross-sectional	Change over time	Change due to the risk model
Global cognitive function									
FSRP									
Low	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Medium	-0.026 (0.098) 0.32	0.109 (0.019) <0.001	0.011 (0.030) 0.71	-0.033 (0.111) 0.77	0.129 (0.015) <0.001	-0.031 (0.021) 0.15	0.029 (0.091) 0.75	0.018 (0.029) 0.54	-0.069 (0.041) 0.09
High	-0.083 (0.093) 0.37	0.109 (0.019) <0.001	0.024 (0.031) 0.43	0.159 (0.115) 0.17	0.129 (0.015) <0.001	-0.015 (0.023) 0.53	-0.052 (0.097) 0.59	0.018 (0.029) 0.54	0.043 (0.046) 0.36
CAIDE									
Low	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Medium	0.071 (0.105) 0.50	0.109 (0.021) <0.001	-0.018 (0.035) 0.60	0.126 (0.128) 0.33	0.102 (0.012) <0.001	**0.057 (0.025) 0.02**	0.053 (0.088) 0.54	0.008 (0.026) 0.76	-0.011 (0.040) 0.99
High	0.123 (0.103) 0.23	0.109 (0.021) <0.001	0.053 (0.037) 0.15	**0.493 (0.112) <0.001**	0.102 (0.012) <0.001	0.001 (0.022) 0.99	**0.348 (0.109) 0.001**	0.008 (0.026) 0.76	-0.032 (0.054) 0.54
Oxi-inflammatory load									
Low	-0.148 (0.138) 0.28	0.118 (0.014) <0.001	0.022 (0.041) 0.60	0.060 (0.147) 0.68	0.118 (0.010) <0.001	-0.023 (0.031) 0.45	-	-	-
Medium	0.0	0.0	0.0	0.0	0.0	0.0			
High	0.20 (0.121) 0.10	0.118 (0.014) <0.001	-0.018 (0.047) 0.70	**0.320 (0.127) 0.01**	0.118 (0.010) <0.001	0.007 (0.033) 0.83			

Abbreviations: CAIDE, Cardiovascular risk factors, Aging and Dementia model; CVD, cardiovascular disease; FSRP, Framingham stroke risk profile. Global cognitive function measured by the Mini-Mental State Examination in all studies. Cognitive tests that were not normally distributed were transformed. Oxi-inflammatory load represents a sum score of the three biomarkers: standardised z-scores for each log transformed biomarker were calculated and the sums of these scores were then determined to create an oxi-inflammatory load. Categories based on tertiles for the FSRP and CAIDE models and for the oxi-inflammatory load: low represents $<10^{th}$ percentile, middle represents 10^{th}-90^{th} percentile and high represents $>90^{th}$ percentile. For the non-MMSE measurements, impairment was defined as a score 1.5 standard deviations below (or above where higher scores indicate worse performance) the mean score. Where scores were not normally distributed this was calculated as the 93^{rd} percentile for scores where higher numbers reflect worse cognitive function, and the 7^{th} percentile for scores where lower numbers reflect worse cognitive function. Oxi-inflammatory load models adjusted for sex, years of education, current alcohol consumption and smoking status.

Table 4. Cox proportional hazard model results (HR and 95%CI) of the association between the FSRP and the CAIDE models, oxi-inflammatory load and incident domain-specific cognitive impairment after follow-up for the Newcastle 85+ study and Leiden 85-plus Study.

	Newcastle 85+ study		**Leiden 85-plus Study**	
	HR (95% CI)	*P*	HR (95% CI)	*P*
Attention				
FSRP				
Low	1.0		1.0	
Medium	0.99 (0.71, 1.38)	0.97	0.94 (0.67, 1.30)	0.69
High	1.27 (0.95, 1.70)	0.11	1.31 (0.94, 1.81)	0.11
CAIDE				
Low	1.0		1.0	
Medium	0.89 (0.61, 1.28)	0.53	**1.57 (1.11, 2.23)**	**0.01**
High	1.25 (0.89, 1.76)	0.20	1.16 (0.82, 1.63)	0.40
Oxi-inflammatory load				
Low	**0.56 (0.33, 0.94)**	**0.01**	0.80 (0.45, 1.43)	0.45
Medium	1.0		1.0	
High	**1.58 (1.05, 2.36)**	**0.03**	**2.18 (1.27, 3.74)**	**0.01**
Memory				
FSRP				
Low	1.0		1.0	
Medium	0.77 (0.40, 1.50)	0.45	1.22 (0.60, 2.46)	0.59
High	0.73 (0.39, 1.36)	0.32	1.14 (0.57, 2.26)	0.72
CAIDE				
Low	1.0		1.0	
Medium	1.01 (0.49, 2.17)	0.97	1.02 (0.40, 2.60)	0.97
High	1.17 (0.56, 2.44)	0.68	0.86 (0.46, 1.63)	0.65
Oxi-inflammatory load				
Low	0.79 (0.34, 1.85)	0.59	0.65 (0.22, 1.90)	0.43
Medium	1.0		1.0	
High	1.11 (0.44, 2.80)	0.83	3.87 (0.84, 17.9)	0.08
Speed				
FSRP				
Low	1.0		1.0	
Medium	1.11 (0.79, 1.55)	0.54	1.00 (0.60, 1.68)	0.98
High	**1.42 (1.06, 1.91)**	**0.02**	0.98 (0.55, 1.75)	0.96
CAIDE				
Low	1.0		1.0	
Medium	0.83 (0.57, 1.21)	0.34	1.42 (0.75, 2.68)	0.28
High	1.18 (0.83, 1.68)	0.35	0.97 (0.54, 1.72)	0.91
Oxi-inflammatory load				
Low	0.65 (0.39, 1.08)	0.10	0.78 (0.30, 2.01)	0.61
Medium	1.0		1.0	
High	**1.85 (1.24, 2.75)**	**0.003**	1.85 (0.43, 7.87)	0.41

Abbreviations: CAIDE, Cardiovascular risk factors, Aging and Dementia model; CVD, cardiovascular disease; FSRP, Framingham stroke risk profile. Oxi-inflammatory load represents a sum score of the three biomarkers: standardised z-scores for each log transformed biomarker were calculated and the sums of these scores were then determined to create an oxi-inflammatory load. Newcastle 85+: Memory was measured using the sensitivity index for recognition ability (SI), attention was measured using power of attention (PoA) and speed was measured using simple reaction time (SRT), all part of the Cognitive Drug Research (CDR) computerised assessment system. Leiden 85-plus Study: Memory was measured using the Word-Learning Test, Immediate and Delayed Recall, attention was measured using the Stroop Test Part 3 and speed was measured using the Letter Digit Coding Test. Categories based on tertiles for the FSRP and CAIDE models and for the oxi-inflammatory load: low represents $<10^{th}$ percentile, middle represents 10^{th}-90^{th} percentile and high represents $>90^{th}$ percentile. For the non-MMSE measurements, impairment was defined as a score 1.5 standard deviations below (or above where higher scores indicate worse performance) the mean score. Where scores were not normally distributed this was calculated as the 93^{rd} percentile for scores where higher numbers reflect worse cognitive function, and the 7^{th} percentile for scores where lower numbers reflect worse cognitive function. Oxi-inflammatory load models adjusted for sex, years of education, current alcohol consumption and smoking status.

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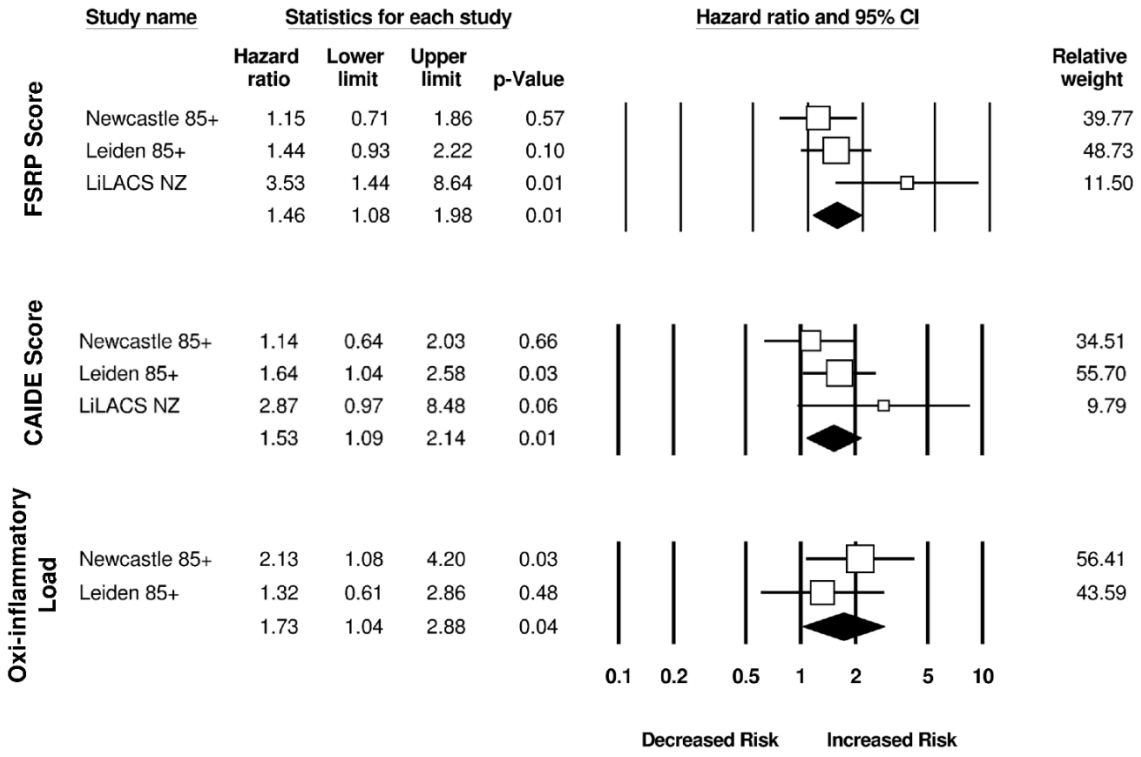

Oxi-inflammatory load represents a sum score of the three biomarkers: standardised z-scores for each log transformed biomarker were calculated and the sums of these scores were then determined to create an oxi-inflammatory load. The LiLACS NZ study did not measure homocysteine and therefore was not included in the oxi-inflammatory load meta-analysis.